The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 16, 2021

VOL. 385 NO. 12

Effect of Salt Substitution on Cardiovascular Events and Death

B. Neal, Y. Wu, X. Feng, R. Zhang, Y. Zhang, J. Shi,* J. Zhang, M. Tian, L. Huang, Z. Li, Y. Yu, Y. Zhao, B. Zhou, J. Sun, Y. Liu, X. Yin, Z. Hao, J. Yu, K.-C. Li, X. Zhang, P. Duan, F. Wang, B. Ma, W. Shi, G.L. Di Tanna, S. Stepien, S. Shan, S.-A. Pearson, N. Li, L.L. Yan, D. Labarthe, and P. Elliott

ABSTRACT

BACKGROUND

Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain.

METHODS

We conducted an open-label, cluster-randomized trial involving persons from 600 villages in rural China. The participants had a history of stroke or were 60 years of age or older and had high blood pressure. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke, the secondary outcomes were major adverse cardiovascular events and death from any cause, and the safety outcome was clinical hyperkalemia.

RESULTS

A total of 20,995 persons were enrolled in the trial. The mean age of the participants was 65.4 years, and 49.5% were female, 72.6% had a history of stroke, and 88.4% a history of hypertension. The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; $P=0.006$), as were the rates of major cardiovascular events (49.09 events vs. 56.29 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.80 to 0.94; $P<0.001$) and death (39.28 events vs. 44.61 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; $P<0.001$). The rate of serious adverse events attributed to hyperkalemia was not significantly higher with the salt substitute than with regular salt (3.35 events vs. 3.30 events per 1000 person-years; rate ratio, 1.04; 95% CI, 0.80 to 1.37; $P=0.76$).

CONCLUSIONS

Among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt. (Funded by the National Health and Medical Research Council of Australia; SSaSS ClinicalTrials.gov number, NCT02092090.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wu at Peking University Clinical Research Center, Peking University, 38 Xueyuan Rd., Haidian District, Beijing, China, or at wuyf@bjmu.edu.cn, or to Dr. Tian at the George Institute for Global Health at Peking University Health Science Center, Rm. 052A, Unit 1, Tayuan Diplomatic Office Bldg., No. 14 Liangmahe Nan Lu, Chaoyang District, Beijing, China, or at mtian@georgeinstitute.org.cn.

*Deceased.

Drs. Neal and Wu contributed equally to this article.

This article was published on August 29, 2021, at NEJM.org.

N Engl J Med 2021;385:1067-77.

DOI: 10.1056/NEJMoa2105675

Copyright © 2021 Massachusetts Medical Society.

ELEVATED DIETARY SODIUM CONSUMPTION, as well as low levels of dietary potassium intake, is associated with high blood pressure and an increased risk of cardiovascular disease and premature death.¹⁻³ Randomized trials of dietary sodium reduction,⁴ as well as trials of dietary potassium supplementation,⁵ have shown clear blood-pressure-lowering effects. Salt substitutes, which replace part of the sodium chloride in regular salt with potassium chloride, combine these effects in a single product.⁶ Salt substitutes are available in many countries worldwide⁷ and have proven blood-pressure-lowering effects in diverse populations.⁶ However, in the absence of well-powered, randomized, controlled trials, there are uncertainties about the effects of salt substitutes on serious disease outcomes such as stroke, acute coronary syndrome, and death. In addition, concern about the theoretical risks of hyperkalemia and associated sudden death from the use of salt substitutes in patients with serious kidney disease has adversely influenced perceptions of clinicians and the general population.⁶ The Salt Substitute and Stroke Study (SSaSS)⁸ was designed to define the overall balance of benefits and risks of salt substitute as compared with regular salt on stroke, cardiovascular events, death, and clinical hyperkalemia.

METHODS

TRIAL DESIGN AND OVERSIGHT

Participants were enrolled in the current trial from April 2014 through January 2015. The SSaSS was an open-label, cluster-randomized trial that was conducted in 600 villages in the rural areas of five provinces in China — Hebei, Liaoning, Ningxia, Shanxi, and Shaanxi. The provinces were selected on the basis of established collaborations with local academic and government institutions. Two counties within each province were chosen according to their willingness to participate, their proximity to the local research team, and their being broadly representative of the level of socioeconomic development in the rural counties in the province. In each of the 10 counties, 60 villages were recruited through a group consent process that involved the leadership of each village and the local county bureaus of health. The goal was to recruit approximately 35 persons from each village and to follow each participant for 5 years. The trial was approved by

the ethics committees at the Peking University Health Science Center in China and the University of Sydney in Australia, and all participants provided written informed consent.

The trial was scheduled to be completed in the first quarter of 2020, but completion was delayed until the first quarter of 2021 because of the coronavirus disease 2019 pandemic and regulatory requirements in China. The scheduled final 5-year follow-up visits were conducted later than planned for about a fifth of participants, but use of the assigned substitute or regular salt was continued during this period. The trial was sponsored by the George Institute for Global Health, where the analyses were performed. The statistical analysis plan, which is provided with the protocol (available with the full text of this article at NEJM.org), was finalized and posted before unblinding of the data. The first draft of the manuscript was written by the first author, and all the authors participated in the subsequent revisions and the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Participants were adult men and women who had a history of stroke or were 60 years of age or older and had poorly controlled blood pressure (systolic blood pressure ≥ 140 mm Hg if receiving blood-pressure-lowering medication or ≥ 160 mm Hg if not). Participants were required to provide personal identifiers and could be contacted by telephone or through a friend or relative whom they had nominated. Persons were excluded if they or someone living in their household had a potential contraindication to the salt substitute used in the trial; contraindications included use of a potassium-sparing diuretic, use of a potassium supplement, or known serious kidney disease. Routine biochemical measurement of kidney function was not performed. Persons were also ineligible if they were considered to be unlikely to live longer than 6 months or ate most meals outside of the home.

RANDOMIZATION AND FOLLOW-UP

Villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute, or to the control group, in which the participants continued to use regular

salt. Randomization was stratified according to county with the use of a central computerized process. Random assignment of the villages was performed only after all the participants in the province had been recruited and all baseline survey data had been collected. Participants in the intervention villages were provided reduced-sodium salt substitute free-of-charge as a replacement for regular salt. The salt substitute was manufactured in accordance with the Chinese national standard and had a composition of 75% sodium chloride and 25% potassium chloride. Sufficient salt substitute was provided to cover all household cooking and food preservation requirements at an average of approximately 20 g per person per day. Participants were advised to use the salt substitute instead of regular salt for all cooking, seasoning, and food preservation purposes and were encouraged to use the salt substitute more sparingly, and not more frequently, than they had previously used salt to maximize the reduction in sodium achieved. Participants in the control villages continued to use regular salt as they usually would. General health advice about stroke prevention, which included a recommendation to reduce salt intake, was provided at trial commencement to all villages but was not reinforced thereafter. Use of other medical therapy was permitted according to local guidelines.

Follow-up was conducted at 6-month intervals and focused on the identification of trial outcomes, hospitalizations, and other serious illnesses. If a possible trial outcome was identified, then additional information was collected by asking participants to complete a structured questionnaire, by photographing documentation held by the participant or family members, and by seeking data from any medical facilities that the participant had visited during the illness. Supplementary data were also sought from the New Rural Cooperative Medical Scheme,⁹ the County Center for Disease Prevention and Control, and the Public Security Bureau as appropriate. Scheduled follow-up visits during the first 2 years after randomization and the final 5-year visit were conducted in person for all participants. In the intervals between visits, potential events were identified only through linkage to databases of routinely collected health insurance records held within the New Rural Cooperative Medical Scheme and National Mortality Surveillance System.¹⁰

During years 3 and 4, only persons with potential trial outcome events were seen face-to-face in order to collect additional information for adjudication of the event. The exception was Changzhi county in Shanxi province, where in-person follow-up visits were conducted at 6-month intervals throughout the trial period. Every 12 months, a targeted subgroup of participants from between 54 and 140 villages were visited to measure 24-hour urinary electrolyte excretion, blood pressure, and adherence to the assigned use of substitute or regular salt.¹¹

OUTCOMES

The primary outcome was stroke, which was defined as an acute disturbance of focal neurologic function resulting in death or symptoms lasting more than 24 hours.¹² Secondary outcomes were major adverse cardiovascular events (a composite of nonfatal stroke, nonfatal acute coronary syndrome, or death from vascular causes) and death from any cause. The safety outcome was clinical hyperkalemia; sudden death was also assessed as a key indicator of safety. Routine serum potassium measurements were not performed. Imaging, clinical, and laboratory data regarding primary, secondary, and safety outcomes were collected whenever possible. All potential efficacy and safety outcome events were reviewed by an end-point adjudication committee, according to standardized definitions provided in an end-point adjudication charter (see the Supplementary Appendix, available at NEJM.org); the members of the committee were unaware of the trial-group assignments. Potential outcome events were assigned causes and were further classified as definite, probable, possible, or unlikely, according to the information contained in the supporting evidence. Primary analyses included data from participants who had definite or probable outcome events. The exception was the safety outcome of clinical hyperkalemia; only two events were classified as definite or probable, and a post hoc decision was made to also include possible events in the analysis.

STATISTICAL ANALYSIS

We estimated that a sample size of 21,000 participants in 600 clusters (300 in the salt-substitute group and 300 in the regular-salt group, with 35 participants in each cluster) would provide the trial with 90% power to detect a proportional

difference of 13% or more in the rate of stroke between the participants who used the salt substitute and those who used regular salt at a two-sided alpha level of 0.05.⁸ Primary analyses were performed according to the intention-to-treat principle. Adjustment for clustering was made with the use of a hierarchical Poisson regression model, with follow-up time as an offset; rate ratios, 95% confidence intervals, and P values were used to compare the effects of the salt substitute and regular salt. Follow-up continued up to the date of the scheduled final 5-year follow-up visit (at which time vital status was determined for all participants) or to the date of death, whichever occurred first. With respect to nonfatal events, the completeness of follow-up was calculated on the basis of the date of death (as determined from a search of health insurance records

Figure 2 (facing page). Effects of Salt Substitution on Blood Pressure and 24-Hour Urinary Sodium and Potassium Excretion.

Systolic (Panel A) and diastolic (Panel B) blood pressure was measured in all participants at baseline, and the differences in blood pressure for each year were derived from paired comparisons that were adjusted for clustering. Twenty-four hour urinary sodium (Panel C) and potassium (Panel D) excretion were measured in only a subgroup of participants at baseline and at each year of follow-up, and the differences for each year were derived from unpaired comparisons in an analysis of covariance adjusted for clustering. Overall differences were calculated with a fixed-effect, inverse-variance-weighted meta-analysis of the differences at each year of follow-up. The size of the boxes is proportional to the inverse variance of the effect estimates. To convert the values for sodium to milligrams, multiply by 23, and to convert the values for potassium to milligrams, multiply by 39.

of all deceased participants), the date of the final in-person follow-up visit, the date of final contact with a family member or other nominated contact, or the date of the final search of routinely collected health data, whichever represented the longest period from randomization. Adjustment for multiplicity in the analyses of the primary and secondary outcomes was performed post hoc with the use of the Benjamini–Hochberg method. Cumulative event curves were generated with the use of the Kaplan–Meier method. Summary effects on continuous outcomes were determined from a fixed-effect, inverse-variance-weighted meta-analysis of the differences at each year of follow-up, which were estimated on the basis of an analysis of covariance that allowed for clustering. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

A total of 20,995 persons were recruited from 600 villages and were assigned to a trial group; 4172 died during the trial. Among the living participants, 15,130 were seen face-to-face at the scheduled final follow-up visit, 1357 had final follow-up through communication with a nominated contact, 317 had final follow-up through record linkage that was completed 2 to 67 weeks before the scheduled final follow-up, and 19 had

a final in-person follow-up visit 23 to 51 weeks before the scheduled time. Vital status was determined for all the participants. Nonfatal events were assessed among the participants for 99,473

of 99,522 person-years (>99.9%) of scheduled follow-up (Fig. 1), and the overall mean and median durations of follow-up were 4.74 and 5.12 years, respectively. At the 5-year follow-up, 91.7% of

the participants in the salt-substitute group and 6.4% of those in the regular-salt group reported using a salt substitute.

Among the participants at baseline, the mean age was 65.4 years, 49.5% were female, 72.6% had a history of stroke, and 88.4% reported having received a diagnosis of hypertension. The mean blood pressure was 154.0/89.2 mm Hg, and 79.3% of the participants were using at least one blood-pressure-lowering medication — 41.8% were using a calcium antagonist, 22.8% an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, 11.5% a diuretic, 5.7% a beta-blocker, and 0.9% an alpha-blocker. The mean 24-hour urinary sodium excretion was 4.3 g (187 mmol), and the mean 24-hour urinary potassium excretion was 1.4 g (36 mmol). Baseline characteristics were balanced between the trial groups (see the Supplementary Appendix).

INTERMEDIATE MARKERS OF CARDIOVASCULAR RISK

Across the follow-up period, the mean difference in 24-hour urinary sodium excretion between the salt-substitute group and the regular-salt group was -350 mg (95% confidence interval [CI], -545 to -154) (-15.2 mmol; 95% CI, -23.7 to -6.7), and the mean difference in 24-hour urinary potassium excretion was 803 mg (95% CI, 714 to 897) (20.6 mmol; 95% CI, 18.3 to 23.0). The mean difference in systolic blood pressure was -3.34 mm Hg (95% CI, -4.51 to -2.18) (Fig. 2).

CARDIOVASCULAR OUTCOMES AND DEATH

The rate of fatal or nonfatal stroke events was significantly lower in the salt-substitute group than in the regular-salt group (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% CI, 0.77 to 0.96; $P=0.006$) (Table 1 and Fig. 3). Point estimates of the effects of the salt substitute and regular salt favored the salt substitute with respect to all predefined exploratory outcomes of stroke (Table 1). The effects of the salt substitute and regular salt on stroke consistently favored the salt substitute across a broad range of prespecified participant subgroups (Fig. 4). As compared with regular salt, the salt substitute was also shown to protect against the secondary outcomes of major adverse cardiovascular events (49.1 events vs. 56.3 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.80 to 0.94; $P<0.001$) and death from any cause (39.3 events

vs. 44.6 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; $P<0.001$) (Table 1 and Fig. 3). The salt substitute was also shown to be beneficial with respect to death from vascular causes (22.9 events vs. 26.3 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.79 to 0.96) and nonfatal acute coronary syndrome (3.8 events vs. 5.1 events per 1000 person-years; rate ratio, 0.70; 95% CI, 0.52 to 0.93) but not with respect to nonfatal stroke (22.4 events vs. 24.9 events per 1000 person-years; rate ratio, 0.90; 95% CI, 0.80 to 1.01) (Table 1). Point estimates of the effects of the salt substitute and regular salt favored the salt substitute with respect to all exploratory outcomes of death (Table 1).

SAFETY OUTCOMES

There were two participants who had definite or probable hyperkalemia (one in the salt-substitute group and one in the regular-salt group). An additional 313 participants, including 302 who died and 11 who had a nonfatal event, were identified as having possible hyperkalemia. There was no evidence of a significant difference between the trial groups in the analyses that included data from participants who had definite, probable, or possible hyperkalemic events, either in the overall population (3.35 events vs. 3.30 events per 1000 person-years; rate ratio, 1.04; 95% CI, 0.80 to 1.37; $P=0.76$) or in any participant subgroup (see the Supplementary Appendix).

DISCUSSION

In the present trial, the participants who received the salt substitute had significantly lower rates of stroke, major adverse cardiovascular events, and death from any cause than those who received regular salt. The observed benefits from the salt substitute were broadly consistent across participant subgroups and prespecified exploratory outcome analyses of stroke, other vascular events, and death. Use of the salt substitute was not associated with any apparent serious adverse effects.

The sizes of the effects on outcomes of stroke observed in our trial are in keeping with our power estimates at trial inception and are in accordance with a mechanism of action mediated through blood-pressure reduction.⁸ The observed changes in 24-hour urinary sodium and potas-

Table 1. Effects of Salt Substitution on Cardiovascular Outcomes and Death.*

Outcome	Salt Substitute	Regular Salt	Rate Ratio (95% CI)
	<i>no. of events per 1000 person-years</i>		
Stroke	29.14	33.65	0.86 (0.77–0.96)
Fatal	6.78	8.79	0.77 (0.65–0.91)
Nonfatal	22.36	24.86	0.90 (0.80–1.01)
Ischemic	21.36	22.90	0.93 (0.82–1.05)
Hemorrhagic	4.37	6.30	0.69 (0.56–0.85)
Undetermined	3.41	4.45	0.76 (0.61–0.96)
Fatal or disabling	12.71	15.04	0.84 (0.73–0.97)
Nonfatal and nondisabling	9.14	9.33	0.99 (0.82–1.91)
Nonfatal and unknown severity	7.30	9.27	0.79 (0.67–0.92)
Definite	9.43	11.62	0.81 (0.70–0.94)
Probable	19.71	22.03	0.89 (0.78–1.02)
Possible	95.60	103.41	0.92 (0.85–0.99)
Nonfatal acute coronary syndrome	3.79	5.12	0.70 (0.52–0.93)
Death from any cause	39.28	44.61	0.88 (0.82–0.95)
Undetermined	8.58	9.58	0.89 (0.75–1.06)
Nonvascular	7.76	8.73	0.89 (0.77–1.03)
Vascular	22.94	26.30	0.87 (0.79–0.96)
Fatal ischemic stroke	1.78	2.23	0.77 (0.55–1.07)
Fatal hemorrhagic stroke	2.55	3.38	0.75 (0.58–0.98)
Fatal undetermined type of stroke	2.45	3.18	0.77 (0.58–1.01)
Death from acute coronary syndrome	2.53	2.53	1.00 (0.75–1.32)
Fatal heart failure	1.10	1.30	0.88 (0.55–1.43)
Kidney-related death	0.32	0.34	0.97 (0.24–3.94)
Other known vascular causes	1.20	1.58	0.72 (0.45–1.14)
Sudden death from presumed vascular causes	11.01	11.76	0.94 (0.82–1.07)

* Some participants had more than one outcome.

sium excretion are of a magnitude consistent with the measured decline in systolic blood pressure. Sodium reduction and potassium supplementation have been shown to independently lower blood pressure and to have synergistic effects.^{4,5,13,14} Although a systematic review and meta-analysis of other studies showed larger effects of salt substitution on blood pressure, all of these studies were of shorter duration than the current trial.¹⁵ Incomplete adherence to the use of the salt substitute, consumption of regular salt outside the home, and some use of a salt substitute in the control group probably attenu-

ated the magnitude of the treatment effects in the current trial.

The absence of any evident increased risk of clinical hyperkalemia addresses concerns about the potential harms from the use of salt substitutes.⁶ Persons at risk of hyperkalemia were excluded if they reported serious kidney disease or the use of medicines that might substantially elevate blood potassium levels. There was no biochemical prescreening of kidney function or potassium levels, and there was concomitant use of drugs blocking the renin–angiotensin system in approximately a quarter of participants. How-

ever, we searched systematically for all serious adverse events potentially attributable to hyperkalemia and did not identify any increased risk of this outcome. We also found no increased risk of sudden death that might be caused by hyperkalemia-induced arrhythmic events. Our data also provide reassurance about the efficacy and safety of sodium-intake reduction for the prevention of cardiovascular events and death. There was no apparent evidence of an increased risk of any cardiovascular or other adverse outcome among the participants, who had a mean baseline 24-hour sodium excretion level of 187 mmol per

day (equivalent to 10.75 g of salt and 4.3 g of sodium), which is only slightly above the average global intake.¹⁶

In the absence of well-powered, randomized, controlled trials, previous attempts to estimate the effects of sodium reduction or potassium supplementation on cardiovascular disease have relied mainly on observational data, which are subject to various biases and confounding.^{17,18} In contrast, the current trial used a robust, randomized design, was large, and had a long duration with many outcome events.

This trial has several notable limitations. Po-

tassium was not measured serially, and elevated potassium levels might have been missed in some participants. Only one preparation of salt substitute was used, and thus graded decreases in sodium intake, which might have induced graded responses, were not evaluated. Although the delivery of the intervention was not concealed, the risk of bias was minimized with the use of objective primary and secondary end points and standardized methods for the identification of outcome events, including ascertainment through systematic searches of routinely collected health data and verification by an independent end-point adjudication committee, the

members of which were unaware of the trial-group assignments. Information that could be used for adjudication of outcome events was limited, and definitive assignment of causation was difficult in many cases. We investigated the potential effect of misclassification of end points on effect estimates but found no evidence that certainty of adjudications had any substantive implications for the primary conclusions of the trial.

We note that the magnitude of protection observed in this trial is similar to that assumed in a recent modeling study that estimated that 365,000 strokes, 461,000 premature deaths, and 1,204,000 vascular events could be averted each

year by the population-wide use of a salt substitute in China.¹⁹ Large benefits might also be achieved in other countries in Asia, Africa, and Latin America in which salt intake is above recommended levels.²⁰ Furthermore, because it is primarily persons in low-income and disadvantaged populations who add large quantities of salt to their diet during food preparation and cooking,²¹ salt substitution — a practical, low-cost intervention (about \$1.62 per kilogram of salt substitute vs. \$1.08 per kilogram of regular salt in China) — may have the potential to reduce health inequities related to cardiovascular disease.

In this trial comparing a salt substitute with

regular salt among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute, which had no apparent serious adverse effects.

Supported by research grants (APP1164206 and APP1049417) and an investigator grant (APP1197709, to Dr. Neal) from the National Health and Medical Research Council of Australia; the salt substitute used in the trial was purchased by the investigators from local manufacturers in each province for years 1, 2, and 5 but was donated by Jiangsu Sinokone Technology for years 3 to 4.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the trial teams and the trial participants.

APPENDIX

The authors' full names and academic degrees are as follows: Bruce Neal, M.B., Ch.B., Ph.D., Yangfeng Wu, M.D., Ph.D., Xiangxian Feng, Ph.D., Ruijuan Zhang, M.Sc., Yuhong Zhang, M.Med., Jingpu Shi, Ph.D., Jianxin Zhang, Ph.D., Maoyi Tian, Ph.D., Liping Huang, Ph.D., Zhifang Li, M.Sc., Yan Yu, Ph.D., Yi Zhao, Ph.D., Bo Zhou, Ph.D., Jixin Sun, M.Sc., Yishu Liu, M.Sc., Xuejun Yin, M.P.H., Zhixin Hao, M.D., Jie Yu, M.D., Ph.D., Ka-Chun Li, M.Sc., Xinyi Zhang, M.P.H., Peifen Duan, M.Sc., Faxuan Wang, Ph.D., Bing Ma, M.Sc., Weiwei Shi, Ph.D., Gian Luca Di Tanna, Ph.D., Sandrine Stepien, M.Sc., Sana Shan, M.Sc., Sallie-Anne Pearson, Ph.D., Nicole Li, M.D., Ph.D., Lijing L. Yan, Ph.D., Darwin Labarthe, Ph.D., and Paul Elliott, M.B., B.S., Ph.D.

The authors' affiliations are as follows: the George Institute for Global Health (B.N., M.T., L.H., Y.L., X.Y., J.Y., K.-C.L., G.L.D.T., S. Stepien, S. Shan) and the Centre for Big Data Research in Health (S.-A.P.), University of New South Wales, and George Clinical (N.L.) — all in Sydney; the School of Public Health (B.N., K.-C.L., P.E.), the U.K. Dementia Research Institute (P.E.), the British Heart Foundation Centre for Research Excellence (P.E.), and the NIHR Imperial Biomedical Research Centre (P.E.), Imperial College London, Health Data Research (P.E.), the NIHR Health Protection Research Unit in Chemical and Radiation Threats and Hazards (P.E.), and the Medical Research Council Centre for Environment and Health (P.E.) — all in London; Peking University Clinical Research Center, Peking University (Y.W.), the George Institute for Global Health at Peking University Health Science Center (Y.W., M.T., Z.H., X.Z., L.L.Y.), and the Department of Cardiology, Peking University Third Hospital (J.Y.), Beijing, the School of Public Health, Changzhi Medical College, Changzhi (X.F., Z.L., P.D.), the School of Public Health, Xi'an Jiaotong University, Xi'an (R.Z., Y.Y.), the School of Public Health and Management, Ningxia Medical University, Yinchuan (Y. Zhang, Y. Zhao, F.W.), the Department of Evidence-Based Medicine, First Hospital of China Medical University, Shenyang (J. Shi, B.Z., B.M.), the Department of Noncommunicable Disease Prevention and Control, Center for Disease Control of Hebei Province, Shijiazhuang (J.Z., J. Sun, W.S.), the School of Public Health, Harbin Medical University, Harbin (M.T.), the Global Health Research Center, Duke Kunshan University, Kunshan (L.L.Y.), and the School of Health Sciences, Wuhan University, Wuhan (L.L.Y.) — all in China; and the Feinberg School of Medicine, Northwestern University, Chicago (D.L.).

REFERENCES

1. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk — measurement matters. *N Engl J Med* 2016;375:580-6.
2. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccino FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ* 2013;346:f1378.
3. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccino FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013;346:f1326.
4. Huang L, Trieu K, Yoshimura S, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ* 2020;368:m315.
5. Filippini T, Naska A, Kasdagli M-I, et al. Potassium intake and blood pressure: a dose-response meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2020;9(12):e015719.
6. Greer RC, Marklund M, Anderson CAM, et al. Potassium-enriched salt substitutes as a means to lower blood pressure: benefits and risks. *Hypertension* 2020;75:266-74.
7. Yin X, Liu H, Webster J, et al. Availability, formulation, labeling, and price of low-sodium salt worldwide: environmental scan. *JMIR Public Health Surveill* 2021;7(7):e27423.
8. Neal B, Tian M, Li N, et al. Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS) — a large-scale cluster randomized controlled trial. *Am Heart J* 2017;188:109-17.
9. Meng Q, Xu K. Progress and challenges of the rural cooperative medical scheme in China. *Bull World Health Organ* 2014;92:447-51.
10. Huang L, Yu J, Neal B, et al. Feasibility and validity of using death surveillance data and SmartVA for fact and cause of death in clinical trials in rural China: a substudy of the China Salt Substitute and Stroke Study (SSaSS). *J Epidemiol Community Health* 2020 December 7 (Epub ahead of print).
11. Huang L, Tian M, Yu J, et al. Interim effects of salt substitution on urinary electrolytes and blood pressure in the China Salt Substitute and Stroke Study (SSaSS). *Am Heart J* 2020;221:136-45.
12. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064-89.
13. Dyer AR, Elliott P, Shipley M. Urinary electrolyte excretion in 24 hours and blood pressure in the INTERSALT Study.

- II. Estimates of electrolyte-blood pressure associations corrected for regression dilution bias. *Am J Epidemiol* 1994; 139:940-51.
14. Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007;356:1966-78.
15. Jafarnejad S, Mirzaei H, Clark CCT, Taghizadeh M, Ebrahimzadeh A. The hypotensive effect of salt substitutes in stage 2 hypertension: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2020;20:98.
16. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol* 2009;38:791-813.
17. He FJ, Campbell NRC, Ma Y, MacGregor GA, Cogswell ME, Cook NR. Errors in estimating usual sodium intake by the Kawasaki formula alter its relationship with mortality: implications for public health. *Int J Epidemiol* 2018;47:1784-95.
18. Cobb LK, Anderson CAM, Elliott P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation* 2014;129:1173-86.
19. Marklund M, Singh G, Greer R, et al. Estimated population wide benefits and risks in China of lowering sodium through potassium enriched salt substitution: modelling study. *BMJ* 2020;369:m824.
20. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1223-49.
21. Bhat S, Marklund M, Henry ME, et al. A systematic review of the sources of dietary salt around the world. *Adv Nutr* 2020; 11:677-86.

Copyright © 2021 Massachusetts Medical Society.

ARTICLE METRICS NOW AVAILABLE

Visit the article page at [NEJM.org](https://www.nejm.org) and click on Metrics to view comprehensive and cumulative article metrics compiled from multiple sources, including Altmetrics. [NEJM.org/about-nejm/article-metrics](https://www.nejm.org/about-nejm/article-metrics).